Articles

The New Macrolides
Azithromycin and Clarithromycin

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Clarithromycin and azithromycin are among the new generation of macrolides that have recently been approved for use. Compared with currently available antibiotics, these agents may be given less frequently and, in the case of azithromycin, for a shorter duration. In vitro data suggest an antimicrobial advantage of both clarithromycin and azithromycin against atypical mycobacterial and toxoplasmal species and possibly *Haemophilus influenzae*. The cost of both these agents is substantially higher than that of erythromycin and doxycycline, although the convenience of single-dose azithromycin is appealing compared with a 7-day course of doxycycline for chlamydial urethritis and cervicitis. These agents appear to offer advantages over erythromycin in the treatment of *Mycobacterium avium-intracellulare*. Additional data are needed to establish their role in other bacterial infections.

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Erythromycin has been widely used in the treatment of pneumonias, including those caused by atypical organisms such as *Legionella pneumophila* and *Mycoplasma pneumoniae*.[1] Many of these pathogens multiply intracellularly and are resistant to standard β-lactam therapy. Erythromycin has limitations, a requirement for frequent doses, distressing gastrointestinal side effects, and reduced effectiveness after exposure to gastric acid.

To improve the spectrum of activity and decrease disadvantages, a new generation of macrolide compounds has been developed. These include azithromycin, clarithromycin, roxithromycin, dirithromycin, micocamycin, and rokitamycin. Azithromycin and clarithromycin have recently been approved by the Food and Drug Administration. Both appear to have more activity against *M pneumoniae, Haemophilus influenzae,* and *Chlamydia trachomatis*, among others, in addition to increased tissue or cellular penetration. They require less frequent dosing and may have fewer severe gastrointestinal side effects than erythromycin. In this review we summarize the pharmacology, spectrum of activity, and clinical use of azithromycin and clarithromycin.

Pharmacokinetics

Azithromycin and clarithromycin are different from the prototypic macrolide, erythromycin (Table 1). Erythromycin is acid labile. In the stomach, it rapidly decomposes to two inactive metabolites, one of which may contribute to the gastrointestinal side effects. As a result of this instability and depending on the salt form, the rate of absorption may be unpredictable (35% ± 25%).[2,3]

Clarithromycin is a 14-membered macrolide similar to erythromycin, whereas azithromycin is a 15-membered compound referred to as an azalide. Structural modifications prevent their degrading in an acid medium, so both have a more predictable oral bioavailability.

TABLE 1.—*Comparative Pharmacokinetic Variables of Erythromycin, Azithromycin, and Clarithromycin**

Variable	Drug and Dose: Erythromycin, 500 mg	Azithromycin, 500 mg	Clarithromycin, 500 mg
Oral bioavailability, %†...	35 ± 25‡	37	55 to 68
Taken with food.....	No	No	Yes
Serum half-life, hr§	1.5 to 3	11 to 14	4.9
Frequency of dosing, ×/day.....	4	1	2
Alter dose in moderate renal failure.....	Yes	No	Yes

*From Gilman et al[2]; Wilson and van Boxtel[3]; Neu[4]; Davey[5]; Ball[11]; and Lode.[12]
†Oral bioavailability refers to the fraction of the parent compound that reaches the systemic circulation.
‡Enteric-coated erythromycin base; absorption is dependent on the salt form and temporal relation to meals.
§The half-life is the time required for the plasma concentration in the body to decline by half.

Clarithromycin is rapidly absorbed from the gastrointestinal tract regardless of when taken and achieves peak serum concentrations in two hours. It has a predictable rate of absorption, and 55% to 68% is available in the serum. Food does not influence its bioavailability but slightly delays the time to peak concentration.[1,3-5] Clarithromycin is metabolized by the liver. One metabolite, 14-hydroxy-clarithromycin, has at least comparable and possibly better antimicrobial activity than the parent com-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CFU = colony-forming units
MIC_{90} = 90% minimal inhibitory concentration

pound.[5] The prolonged half-life of both clarithromycin and its 14-hydroxy metabolite allows for twice-a-day dosing. The renal clearance of clarithromycin and 14-hydroxy-clarithromycin approximates glomerular filtration.[5] Moderate to severe renal failure alters the clearance of both clarithromycin and its 14-hydroxy metabolite so that patients with a creatinine clearance of less than 0.50 ml per second (30 ml per minute) should have doses decreased by half.[6]

Azithromycin, like clarithromycin, is readily absorbed from the gastrointestinal tract and achieves peak serum levels within two hours. The bioavailability of azithromycin is substantially less than that of clarithromycin, about 37% to 40%. Food will decrease the bioavailability of azithromycin as much as 50%, so each dose should be taken at least an hour before or two hours after a meal.[7-9] It is metabolized by the liver, but unlike clarithromycin, its metabolites do not show notable antimicrobial activity. Azithromycin has an unusually long half-life so that once-a-day dosing is possible. High concentrations are achieved in tissue (skin, lungs, sputum, tonsils, and cervix). The extensive intracellular uptake of azithromycin results in a tissue half-life between two and four days.[8] In addition, azithromycin concentrates in polymorphonuclear leukocytes and phagocytes, suggesting that phagocytes may play a role in the transport of the drug to the site(s) of infection.[10] The intestinal tract is the major route of elimination for azithromycin; only 6% to 20% is eliminated renally.[11,12] Therefore, in patients with mild renal dysfunction, dose adjustment is not warranted. In patients with severe renal dysfunction, however, a decrease in dose or frequency of dosing intervals may be indicated.

Antimicrobial Spectrum

As a class, the macrolide antibiotics, specifically erythromycin, clarithromycin, and azithromycin, exert their antimicrobial activity by binding to the 50S subunit of the 70S ribosome, which interferes with protein biosynthesis of susceptible organisms.[1,4,13] Resistance is chromosome or plasmid mediated.

Overall, the microbiologic spectrum of the activity of clarithromycin and azithromycin mirrors that of erythromycin, with increased potency against certain pathogens (Table 2). The new generation of macrolides inhibits viridans streptococci, *Streptococcus pneumoniae,* and group A streptococci at readily achievable concentrations, similar to the action of erythromycin.[1,4,6,12,14,15] Streptococcal and staphylococcal species resistant to erythromycin are likely to be resistant to azithromycin and clarithromycin as well. *Moraxella catarrhalis, M pneumoniae, L pneumophila,* and *Chlamydia pneumoniae* are inhibited by azithromycin and clarithromycin at lower concentrations.

TABLE 2.—*In Vitro 90% Minimal Inhibitory Concentrations (MIC_{90}) of Erythromycin, Azithromycin, and Clarithromycin**

Bacteria	MIC_{90}, mg/liter		
	Erythromycin	Azithromycin	Clarithromycin
Borrelia burgdorferi	0.06	0.015	0.015-0.06
Campylobacter jejuni	1.0	0.12	2.0
Chlamydia pneumoniae	0.06	0.5	0.007
Chlamydia trachomatis	2.0	0.25	0.125
Haemophilus influenzae	2.0-8.0	0.25-2.0	2.0-8.0†
Helicobacter pylori	0.25	0.25	0.03
Legionella pneumophila	2.0	2.0	0.25
Moraxella catarrhalis	0.25	0.06	0.12-0.25
Mycobacterium avium-intracellulare	>64	32->64	4-16
Mycoplasma pneumoniae	≤0.01	<0.01	0.5
Neisseria gonorrhoeae	0.25-0.5	0.03-0.06	0.25-0.5
Staphylococcus aureus	0.25	1.0	0.12
Streptococcus pneumoniae	0.015-0.25	0.015-0.25	0.015-0.06

*From Williams[16]; Brown et al[21]; Preac-Mursic et al[23]; Mursic et al[24]; and Ridgway et al.[25]
†The MIC_{90} of clarithromycin alone; 14-hydroxy, the metabolite, may contribute to antimicrobial activity.

Erythromycin is inactive against most gram-negative organisms (including *Escherichia coli* and *Salmonella, Shigella,* and *Pseudomonas* species). Similarly, both azithromycin and clarithromycin are ineffective against *Pseudomonas* species and most aerobic gram-negative bacilli, but azithromycin exhibits enhanced activity against *H influenzae* when compared with erythromycin. It is unclear whether this increased activity results in a reliable drug against *H influenzae.*[16] In one study, the persistence of *H influenzae* was shown in 5 of 21 patients treated for an exacerbation of acute bronchitis; all 5 patients required alternative antibiotic therapy.[17] Clarithromycin and its 14-hydroxy metabolite also appear to be moderately active against *H influenzae.*[18]

Both azithromycin and clarithromycin show promise in the treatment of atypical pathogens such as *Mycobacterium avium-intracellulare, Mycobacterium chelonei, Mycobacterium fortuitum, Borrelia burgdorferi,* and *Toxoplasma gondii.* Clarithromycin has been shown to inhibit *M avium-intracellulare* at concentrations achieved in both lung tissue and macrophages (90% of minimal inhibitory concentration [MIC_{90}] = 4 to 16 mg per liter), with enhanced activity when used in combination with rifampin and ethambutol hydrochloride.[19,20] Azithromycin is less active than clarithromycin against *M avium-intracellulare,* whereas other atypical pathogens such as *M chelonei* subspecies *chelonei* and *M fortuitum* biovariant *fortuitum* are more susceptible.[16,21] Because of high intracellular concentrations, however, azithromycin may still have in vivo effects against *M avium-intracellulare.*[22] In vitro, azithromycin and clarithromycin are active against *T gondii,* reaching sufficient concentrations in the cerebrospinal fluid to kill both active organisms and cysts.[6,16] Like erythromycin, both azithromycin and clarithromycin have shown in vitro activity against *B burgdorferi,* achieving an MIC_{90} of 0.015 and 0.015 to 0.06 mg per liter, respectively.[6,23,24] Because of their favorable kinetics and in

vitro efficacy, both azithromycin and clarithromycin warrant further evaluation in the treatment of mycobacterial infection, toxoplasmosis, and Lyme disease.

In vitro susceptibility of *C pneumoniae* (TWAR) to clarithromycin was compared with that of erythromycin, oxytetracycline, and the other new-generation macrolides.[25] Clarithromycin was found to be the most active, followed by erythromycin and azithromycin. Again, comparative controlled studies need to be done to confirm these in vitro findings.

Finally, both azithromycin and clarithromycin have shown in vitro activity against certain sexually transmitted diseases. Thus far, azithromycin has demonstrated moderate to excellent activity against *C trachomatis, Neisseria gonorrhoeae,* and *Ureaplasma urealyticum,* with cure rates of 91% to 97%.[26,27] Both azithromycin and clarithromycin have excellent in vitro activity against *Haemophilus ducreyi.* Clarithromycin has also shown in vitro bactericidal activity against *C trachomatis* and variable activity against *N gonorrhoeae.*

Clinical Trials

Clarithromycin

Clarithromycin has been evaluated in the treatment of several infectious diseases, including mild to moderate respiratory tract infection, skin or soft tissue infection, and infections due to *M avium-intracellulare* and *T gondii.* Its use has been compared with that of a number of agents—erythromycin, ampicillin, amoxicillin, and penicillin VK—in the treatment of community-acquired pneumonia, pharyngitis, or acute exacerbation of chronic bronchitis.[1,28] Two studies comparing clarithromycin with penicillin VK and one study comparing clarithromycin with erythromycin in the treatment of streptococcal pharyngitis showed clinical cure rates of 96% for clarithromycin and 89% to 96% for the other two agents. In comparative studies, clarithromycin was found to be well tolerated with no significant difference in the overall number of adverse events reported. In the erythromycin-treated group, however, a higher incidence of adverse drug reactions was observed, with 6.7% of patients requiring the discontinuation of therapy compared with 0.8% in the clarithromycin-treated group.[29-31]

Hamedani and co-workers studied 46 patients with confirmed *L pneumophila* pneumonia who were given clarithromycin, 500 to 1,000 mg orally twice a day for four weeks.[32] Of the 46 patients, 44 (96%) had received one or more antibiotics before study entry. Nearly three fourths (34) completed the study and were assessed for clinical and radiographic cure; bacteriologic cure was assessed in only 13 patients. A 98% cure rate was reported in the 34 patients who completed therapy. These results suggest that clarithromycin may be effective, but they need to be confirmed in larger controlled, comparative studies.

Cassell and colleagues conducted a double-blind, randomized, multicenter clinical trial comparing the use of clarithromycin with that of erythromycin in patients with community-acquired pneumonia.[33] A total of 120 patients received clarithromycin or erythromycin for 14 days. Clarithromycin and erythromycin were equally effective in the treatment of community-acquired pneumonia, with clinical cure rates of 83% and 87%, respectively. The frequency of adverse effects did not differ between the groups. The incidence of gastrointestinal side effects (vomiting, nausea, diarrhea, and dyspepsia), however, was greater for the erythromycin group (9 patients) than for those treated with clarithromycin (4 patients).

The safety and efficacy of clarithromycin have been evaluated in the treatment of skin or soft tissue infection.[22,34] One comparative trial involved 439 patients with pyoderma, cellulitis, wound infection, abscess, or folliculitis; causative agents included *Staphylococcus aureus* and *Staphylococcus pyogenes.*[22] Treatment with clarithromycin, erythromycin, or cefadroxil similarly cured or improved all groups of patients.

Clarithromycin appears promising in the treatment of disseminated *M avium-intracellulare.* In a randomized, placebo-controlled study, Dautzenberg and associates evaluated the ability of clarithromycin to decrease *M avium-intracellulare* bacteremia in patients with the acquired immunodeficiency syndrome (AIDS).[35] Fifteen patients were randomly assigned to one of two groups: group 1 was given clarithromycin, 1,000 mg orally twice a day for six weeks, followed by six weeks of placebo, rifampin, isoniazid, ethambutol, and clofazimine; group 2 was given placebo for only six weeks, followed by six weeks of clarithromycin plus the other four agents. The major determinant of efficacy was the quantitative difference of *M avium-intracellulare* colony-forming units (CFU) in blood between the two groups. During phase I, blood cultures of seven of the eight patients receiving clarithromycin alone (group 1) became negative for *M avium-intracellulare* between weeks 2 and 4; one patient consistently had weakly positive blood cultures throughout this phase. The mean decrease in *M avium-intracellulare* bacteremia was 2.65 log. When these patients were switched to placebo plus the four-drug regimen, the blood concentration of *M avium-intracellulare* increased in four patients and remained undetectable in three patients. In the group initially treated with placebo (group 2), all five patients showed an increase in mean levels of *M avium-intracellulare* CFU by 1.55 log over six weeks. When group 2 patients were crossed over to clarithromycin plus the four-drug regimen, however, the mean *M avium-intracellulare* CFU levels of all patients decreased by 1.34 log over the six-week period. In another recent study by Dautzenberg and colleagues, the efficacy and antimycobacterial activity of high-dose clarithromycin (1,500 to 2,000 mg per day) were compared with those of low-dose clarithromycin (500 to 1,000 mg per day) in the treatment of disseminated *M avium-intracellulare.*[36] Bacteriologic cure was achieved in 63% and 98% of the patients in the low- and high-dose groups, respectively. An overall failure rate of 25% was seen between months 2 and 7 of treatment, however.

The use of clarithromycin in combination with pyrimethamine has been evaluated for the treatment of

acute toxoplasmal encephalitis in a study of 13 AIDS patients.[37] Clarithromycin, 2 grams per day, and pyrimethamine, 75 mg per day, were used. Eight patients completed the six-week regimen. Complete remission was defined as a resolution of all clinical or radiologic manifestations. Partial response was defined as 50% or more improvement of clinical or radiologic manifestations. Patients were evaluated at weeks 3 and 6; a complete remission of clinical symptoms was noted in six of eight patients (80%) and a partial response in two of eight patients (20%). The radiographic findings were less conclusive. In eight patients completing the course, a complete response was seen in one, a partial response in three, and an incomplete response in four patients. Mild nausea, vomiting, or skin rash (or all 3) occurred with the highest frequency (38%); these patients required no modification in their therapy. Two patients (15%) had clinical hearing loss that continued as long as two weeks after clarithromycin was discontinued. These data are comparable to the results reported for pyrimethamine plus sulfadiazine and pyrimethamine plus clindamycin.[38]

Azithromycin

The efficacy of azithromycin has been demonstrated in a limited number of clinical studies involving the treatment of sexually transmitted diseases, soft tissue infections, mild to moderate respiratory tract infection, and *M avium-intracellulare*.[22,26,39,40] Studies of animals suggest that azithromycin also may have a role in the treatment of *T gondii*.[41]

Considering its long pharmacologic half-life, azithromycin is promising in the treatment of infection due to *C trachomatis, N gonorrhoeae,* or *U urealyticum*. High levels of azithromycin have been observed as long as 96 hours after the administration of a single 500-mg oral dose, with a prolonged half-life of greater than 60 hours.[8] The maintenance of high tissue concentrations in uterine or cervical tissue may allow for single-dose treatment of pathogens such as *C trachomatis*.

A randomized, double-blind study compared three regimens of azithromycin with a seven-day course of doxycycline in the treatment of *C trachomatis, N gonorrhoeae*, and *U urealyticum*.[26] The doses of azithromycin were as follows: 500 mg orally twice a day for one day; 500 mg a day orally for one day, followed by 250 mg a day orally for two days; or 1 gram for a single dose. Patients were randomly assigned and observed for four weeks. The finding was that 92% of the patients with *N gonorrhoeae* infection and 96% of the patients with chlamydial infection were bacteriologically cured with azithromycin. Azithromycin was well tolerated (8 patients had either mild abdominal pain, nausea, or diarrhea) and may offer an alternative to doxycycline in the treatment of chlamydial infections.

A similar study of 108 patients confirmed the results of that study.[39] Patients with confirmed *N gonorrhoeae* or *C trachomatis* infections or both were treated with single-dose or three-day regimens of azithromycin compared with a seven-day course of doxycycline (100 mg orally twice a day). Single-dose azithromycin treatment was as effective as the standard seven-day doxycycline therapy against *C trachomatis*. It is unclear whether a single 1-gram oral dose may be recommended as an alternative treatment of uncomplicated gonorrhea; ongoing studies are attempting to answer this question.

Comparative trials have evaluated the clinical efficacy of azithromycin in skin or soft tissue infection.[39,42] Treatment with azithromycin (500 mg every 12 hours for 1 day, then 250 mg a day on days 2 to 5) was compared with that of erythromycin (500 mg every 6 hours for 7 days) in 69 patients diagnosed with pyoderma, abscess, or infected wounds, among other infections. Clinical cure or improvement was achieved in 86% of the azithromycin-treated group and 82% of the erythromycin-treated group. Bacteriologic eradication was achieved in about 60% of all patients. *S aureus* was the most common organism isolated.

In a second randomized, third-party-blinded trial, the use of azithromycin was compared with that of cephalexin in the treatment of skin and skin structure infections.[42] The main causative agents in the 361 patients entered in the study were *S aureus* and *S pyogenes*. As in the previously described study, if the pathogens were resistant to therapy or a causative agent was not identified, the patients were withdrawn from the study. Patients were randomly allocated to receive azithromycin, 500 mg orally for one day followed by 250 mg orally a day on days 2 to 5, or cephalexin, 500 mg twice a day for ten days. Of the 149 patients evaluated, clinical cure was achieved in 66.7% of the azithromycin-treated group and 58.7% of the cephalexin-treated group. The bacteriologic cure rate was 98% in both groups. Similar to the previous trial, the large withdrawal rate complicates analysis. Furthermore, the cure rate was not stratified by primary diagnosis. Additional comparative trials are needed to define the usefulness of azithromycin in the treatment of skin and soft tissue infection.

Azithromycin has been compared with other agents in the treatment of upper respiratory tract infections. Azithromycin, 500 mg orally on day 1, followed by 250 mg orally on days 2 to 5, was compared with penicillin VK, 250 mg orally four times a day for ten days, in the treatment of streptococcal pharyngitis.[43] Clinical cure occurred in 86.8% of the patients receiving azithromycin and 78% of the patients taking penicillin VK. Complete eradication of group A β-hemolytic streptococci was achieved in 90% of the azithromycin-treated group and 95% of the penicillin-treated group.

Likewise, a second study evaluated the efficacy of azithromycin (500 mg orally on day 1, followed by 250 mg orally on days 2 to 5) with that of erythromycin (250 mg orally 4 times a day for 10 days) and amoxicillin (500 mg orally 3 times a day for 10 days) in the treatment of sinusitis and other upper respiratory tract infections.[44] Clinical cure was achieved in 82% of the patients receiving azithromycin compared with 79% and 87% of the erythromycin- and amoxicillin-treated pa-

tients, respectively; this included an 89% to 91% eradication of *H influenzae*.

Azithromycin has also been evaluated in the treatment of lower respiratory tract infections. When compared with erythromycin (500 mg orally 4 times a day for 7 to 10 days) or amoxicillin (500 mg orally 3 times a day for 7 days), azithromycin achieved clinical cure rates of 51% to 70% compared with 60% for erythromycin and 45% for amoxicillin.[45] Bacteriologic eradication of the main pathogens (*H influenzae, S pneumoniae*, and *S aureus*) was comparable among the three groups (76% to 85%); this includes an *H influenzae* eradication rate of 81% to 86% (azithromycin) and 78% to 80% (amoxicillin and erythromycin). Adverse effects, the most common of which were nausea, vomiting, and diarrhea, occurred in 5% of all patients treated with azithromycin compared with 18% of the erythromycin-treated patients. Considering the lack of data in the treatment of lower respiratory tract infection, the manufacturer recommends that azithromycin not be used in the following persons: patients with nosocomially acquired infection, patients with known or suspected bacteremia, patients requiring hospital admission, elderly or debilitated patients, and patients who are immunocompromised.

Schönwald and co-workers compared the efficacy of azithromycin with that of erythromycin in the treatment of pneumonia due to *M pneumoniae* and *Chlamydia psittaci*.[40] In that study, 57 patients were treated with azithromycin and 44 patients were treated with erythromycin. The investigators concluded that a five-day regimen of azithromycin was equally efficacious to a ten-day course of erythromycin.

Despite the poor in vitro activity of azithromycin against *M avium-intracellulare* (Table 2), the drug may be effective because of the high tissue concentrations achieved with this agent. In one uncontrolled study, Young and colleagues showed that azithromycin given in doses of 500 mg orally a day for as long as 30 days substantially reduced the degree of mycobacteremia.[22] Although this was a small study (n = 24) and involved single-drug therapy for a short period of time, it suggests the effectiveness of azithromycin in treating *M avium-intracellulare*.

In the murine model, azithromycin therapy has been noted to prevent death due to *T gondii*.[41] The concentration needed to achieve the appropriate MIC_{90} appears to be toxic to host macrophages.[46] Clinical trials using a combination of pyrimethamine and azithromycin are currently under way.[14]

Adverse Effects

Structural modifications of the newer generation of macrolides render them more acid stable, with fewer side effects when compared with erythromycin.[26,32,33,39,40] Gastrointestinal side effects (diarrhea, nausea, abdominal pain, dyspepsia, vomiting, or gastritis) have been reported in 10% to 20% of clarithromycin-treated patients and 10% of azithromycin-treated patients compared with 20% to 35% with erythromycin.[11,28,33] Anderson evaluated adverse effects in 3,437 patients who had received clarithromycin in phase II-III studies and found an incidence of mild to moderate adverse effects; 1% were classified as severe.[28] In the limited number of clinical trials evaluating the efficacy of azithromycin, the incidence of side effects ranged from 0% to 8%, with abdominal pain, nausea, and mild diarrhea the most frequently reported.[26,39,40] Hopkins and associates studied the tolerability and safety profile of azithromycin in approximately 4,000 patients.[9] Side effects were reported in 12% of the patient population. Gastrointestinal side effects (diarrhea, abdominal pain, and nausea) predominated. Central and peripheral nervous system adverse effects (headache, dizziness, fatigue) were noted, but they were mild to moderate in severity.

Anecdotal data suggest that the newer macrolides (especially clarithromycin) may exhibit teratogenic effects. Four unpublished studies of animals using clarithromycin describe adverse effects on embryofetal development. These effects include growth retardation, cleft palate, and cardiac defects. Based on these data, the manufacturer recommends that clarithromycin be used in pregnant women only where no alternative therapy is appropriate.[13]

Likewise, multiple doses of azithromycin have also been tested for teratogenicity in mice and rats.[47] To date, no teratogenicity or effects on fertility have been observed in either species. No studies have been done of pregnant women.

Drug Interactions

Because clarithromycin and azithromycin have only recently gained Food and Drug Administration approval, information regarding clinically important drug interactions is limited (Table 3). The use of erythromycin has been associated with a number of drug interactions involving theophylline, carbamazepine, warfarin sodium, digoxin, and ergotamines.[1,13] The mechanism of action involves the inhibition of drug metabolism by the cytochrome P-450 mixed-oxidase system, thus leading to increased drug concentrations.

Ruff and co-workers, in evaluating the possible interaction between clarithromycin and theophylline, found that clarithromycin increased the mean steady-state theophylline concentration from 86 to 102 μmol per liter.[48] It was concluded that concurrent administration is not an absolute contraindication, but caution must be taken in those patients with concentrations in the upper therapeutic range or in those who are sensitive to minor fluctuations in theophylline levels. Of the 3,437 patients involved in phase II-III trials of clarithromycin, 18% received one or more concomitant medications (not listed) whose oxidative metabolism may have been affected by clarithromycin.[49] There was no increase in the incidence of adverse effects reported in this patient population, with the exception of persons receiving concomitant theophylline; 9 of 492 of these patients had a mild to moderate drug interaction with theophylline.

Azithromycin, like erythromycin, interacts with the cytochrome P-450 system. To date, however, no clinically notable drug interactions have been reported with

TABLE 3.—*Drug Interactions With Erythromycin, Azithromycin, and Clarithromycin**

Interacting Drug	*Erythromycin*	*Azithromycin*	*Clarithromycin*
Digoxin	Increased digoxin levels	Not reported but the potential exists	Not reported but the potential exists
Anticoagulants (warfarin sodium)	Increased therapeutic effects (prothrombin time and international normalized ratio)	Not reported but the potential exists	Not reported but the potential exists
Ergotamines	Possible severe peripheral vasospasm; dysesthesia	Possible severe peripheral vasospasm; dysesthesia	Not reported but the potential exists
Triazolam	Increased pharmacologic effect of triazolam	Not reported but the potential exists	Not reported but the potential exists
Magnesium or aluminum antacids	May increase the half-life of erythromycin	Decreased peak serum levels without affecting the extent of absorption	Not reported but the potential exists
Carbamazepine, phenytoin, cyclosporine, hexobarbital, theophylline	Possible increase in serum levels	Not reported but the potential exists	Phase I studies: demonstrated increased plasma levels of theophylline and carbamazepine

*From Hopkins[9] and the product package insert for Ery-Tab (erythromycin), Abbott Laboratories, North Chicago, Ill.

theophylline, warfarin, carbamazepine, or methylprednisolone sodium succinate.[9,12] Furthermore, in those clinical studies in which azithromycin-treated patients received concomitant medications—bronchodilators, analgesics, corticosteroids, diuretics, hypnotic or sedative anxiolytics, or antiarthritis drugs—no drug interactions were noted. These observations, however, should not preclude the careful monitoring of patients for possible drug-induced interactions. It is unknown whether either azithromycin or clarithromycin interacts similarly to erythromycin with other drugs.

Potentially serious interactions may involve certain highly protein-bound drugs because the macrolide antibiotics extensively bind to the α_1-acid glycoproteins. Theoretically, the displacement of bound drug may result in increased free concentrations and thus an increased pharmacologic effect.

Costs

Whereas the newer macrolides offer the advantages of less frequent dosing and better gastrointestinal tolerability, they are considerably more expensive than erythromycin. Table 4 compares the cost of various treatments with these drugs.

Conclusion and Recommendations

Azithromycin and clarithromycin offer microbiologic advantages over erythromycin, particularly against atypical mycobacteria and *T gondii*. Although the clinical data are limited, these drugs appear to have some use in the treatment of disseminated *M avium-intracellulare* in AIDS patients and as an alternative therapy for central nervous system toxoplasmosis. Whereas azithromycin and clarithromycin appear to be more active against *H influenzae*, it is unclear whether these drugs offer additional benefit over erythromycin. Clinical data are insufficient to establish these drugs as alternatives to combination agents such as trimethoprim-sulfamethoxazole or amoxicillin-clavulanate in the treatment of community-acquired respiratory tract infection due to *H influenzae*. The prolonged half-lives of these agents result in less frequent dosing. This benefit is most obvious for azithromycin in which a single dose is as effective as one week of doxycycline in the treatment of uncomplicated chlamydial cervicitis and urethritis. Limited studies also suggest that five days of azithromycin therapy may be as effective as more prolonged courses of alternative antimicrobials in skin and soft tissue infection and mild respiratory tract infection. The newer agents appear to be better tolerated by the gastrointestinal tract than erythromycin, but the incidence of adverse effects may differ with the salt form of erythromycin. Finally, azithromycin and clarithromycin are more expensive than erythromycin. Until additional clinical data become available, azithromycin and clarithromy-

TABLE 4.—*Dosage Regimens and Comparative Cost**

Dosing Regimens	*Total Cost, $†*
Upper respiratory tract infection	
Sulfamethoxazole-trimethoprim (800/160 mg) 2×/d for 10 d	2.00
Erythromycin, 500 mg every 6 hr for 10 d	10.00
Clarithromycin, 500 mg every 12 hr for 10 d	53.40
Azithromycin, 500 mg a day for 1 d followed by 250 mg a day for 4 d	48.72
Lower respiratory tract infection	
Sulfamethoxazole-trimethoprim (800/160 mg) 2×/d for 10 d	2.00
Erythromycin, 500 mg every 6 hr for 10 d	10.00
Clarithromycin, 500 mg every 12 hr for 10 d	53.40
Azithromycin, 500 mg a day for 1 d, then 250 mg a day on days 2 to 5	48.72
Sexually transmitted diseases	
Doxycycline, 100 mg 2×/d for 7 d	1.96
Azithromycin, 1,000 mg for 1 dose	32.50
Skin or soft tissue infections	
Erythromycin, 500 mg every 6 hr for 7 d	7.00
Cephalexin, 500 mg 4×/d for 10 d	35.60
Clarithromycin, 250 mg 2×/d for 10 d	53.40
Azithromycin, 500 mg for 1 dose, then 250 mg a day for 4 d	48.72

*From the product package inserts of Biaxin (clarithromycin), Abbott Laboratories, North Chicago, Ill, and Zithromax (azithromycin), Pfizer Laboratories, New York, NY.
†Based on the Average Wholesale Price Blue Book.[50]

cin should be considered only in those patients intolerant of erythromycin or doxycycline or in AIDS patients with disseminated *M avium-intracellulare* infection.

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